Age-Related Spatial Reference and Working Memory Deficits Assessed in the Water Maze

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Received 7 February 1994; Revised 1 October 1994; Accepted 1 November 1994

FRICK, K. M., M. G. BAXTER, A. L. MARKOWSKA, D. S. OLTON AND D. L. PRICE. Age-related spatial reference and working memory deficits assessed in the water maze. NEUROBIOLOG AGING 16(2) 149-160, 1995.—Aged rats have spatial memory deficits relative to young rats. The extent of these deficits in intermediate-aged rats is not well established. The present study examined the pattern of age-related changes in spatial reference and working memory in four ages of Fischer-344 rats. Place discrimination (PD) in the Morris water maze measured spatial reference memory. Repeated acquisition (RA), a discrimination in which the escape platform location varied from session to session, measured spatial working memory. Fischer-344 rats, 4 months, 11 months, 17 months, and 24 months of age, were tested. Compared to 4-month-olds, 24-month-olds were significantly impaired on all six PD measures of performance, 17 months were significantly impaired on five PD measures, and 11 months were significantly impaired on only one PD measure. Only 24-month-olds had a significant working memory impairment in RA relative to 4 months. Reference and working memory measures were distinct as assessed by a principal components analysis. The results indicate a nonlinear age-related spatial memory decline in Fischer-344 rats from 4 to 24 months of age.

SENESCENCE in humans is accompanied by impairments in spatial learning and memory (14,49,51). The spatial memory of aged rats is also impaired in various tests of spatial learning and memory such as the circular platform (5), the radial arm maze (11-13,24,25), and the Morris water maze (15,18-21). Both humans and rats exhibit age-related alterations in the hippocampus (5,12,13,15,16,17,25), a structure that is thought to be critical for spatial memory (40,42). Because of these age-related behavioral and neural similarities, spatial memory deficits in aged rats may provide a useful model for the cognitive deficits associated with aging in humans (4).

The water maze is a particularly useful tool for assessment of spatial memory ability in aged rats because it is reliably sensitive to age-related impairments in spatial memory (15,19,21, 22,35). In addition, the water maze is well suited for testing older rats because the motivating stimulus, escape from water, does not require the food or water deprivation that is common in appetitive tests like the radial arm maze or T maze. The nutrient restriction used in these appetitive tasks may endanger the health of aged rats. Another benefit of the water maze is that many aspects of performance can be examined, providing several measures of spatial memory.

Two types of memory that have been studied extensively in young rats are reference memory and working memory (27,28,38,39,40,43,46). The terms “reference” and “working” refer to psychologically distinct mnemonic processes. Reference memory is trial independent (i.e., relevant for many trials, often for an entire experiment) (43). Reference memory is required to learn the general rules of any task (e.g., run to the end of a maze or swim to a platform). Because reference information is consistent from trial to trial, remembering when a particular stimulus was presented is irrelevant. In contrast to reference memory, working memory is trial dependent (i.e., relevant for one trial only) (43). This type of memory has a major temporal component. It is necessary to remember both the type of stimulus presented and the time of stimulus presentation. Working memory is distinguished from reference memory by the transient nature of the stimulus–response relationship.

In the present study, spatial reference and working memory were assessed. In both reference and working memory proce-
durees, memory for spatial locations was crucial because the procedures required a response in relation to salient extramaze cues. Because of the common spatial nature of the tasks, some correlation in performance of the two tasks was expected.

Aged rats have impaired spatial reference memory relative to young rats (15,19,34). Place discrimination (PD) in the water maze is often used to assess spatial reference memory. This procedure requires a rat to locate a submerged platform using spatial cues in the environment (38,39). Aged rats are impaired relative to young rats and are more likely to adopt nonspatial response strategies to escape from the water than are young rats (6,22,48). However, significant individual differences in performance occur within the aged population; some aged rats perform as well as young rats, while others are severely impaired (15,21; see also ref. 47 for a review).

Few spatial working memory tasks have been developed for use in the water maze and some of the procedures that do exist often require several weeks of training to learn (e.g., ref. 36). The present experiment uses repeated acquisition (RA) in the water maze to assess spatial working memory (50). This task is similar procedurally to the standard place discrimination except that the platform location for each test session is different from that in the previous session. The first trial of each session is an information trial in which the rat is allowed to swim to the platform in its new location. The platform remains in the same location throughout the remaining trials of the session. Learning is assessed both within and between sessions to examine both working and reference memory.

The present experiment was designed to examine changes in spatial memory with increasing age. Until recently, most aging studies included only two age groups: "young" and "aged" (e.g., 16,18,19,23,24). Thus, the mnemonic deficits of aged rats are well-characterized, whereas less information is available about memory ability at intermediate ages. Studies limited to two age groups cannot detect patterns or rates of behavioral or neurobiological change throughout life (9). Multiple ages are needed to determine whether age-related alterations are linear or non-linear. Studies using Fischer-344 rats of intermediate ages indicate that these rats may perform spatial tasks at a level between that of young and aged rats (10,34), suggesting a gradual or linear rate for spatial memory change. This experiment used four age groups: 4-, 11-, 17-, and 23- to 24-months old, to describe the effects of age on spatial reference and working memory in rats. These age groups were chosen to represent rats at four different stages of life: young adult, mature adult, middle aged, and aged.

METHOD

Subjects

Male Fischer-344 rats were obtained from the NIA colony at Harlan. The median life span of male Fischer-344 rats in the laboratory is 23 to 29 months (29,30). At the beginning of behavioral testing, the rats were 4 (MO, n = 31), 11 (11MO, n = 18), 17 (17MO, n = 18), and 23- to 24 (24MO, n = 32) months old and were housed 2 to 3 per cage in a colony room with a 12L:12D cycle. Behavioral testing was performed during the light phase of the cycle. Thirteen 4MO rats and twelve 24MO rats were tested as part of other experiments (7,8). Food and water were available ad lib.

Apparatus

The water tank, made of galvanized metal, was 1.8 meters in diameter and 0.6 meters high. It was painted white on the in-side and around the rim. Water filled the tank to a depth of approximately 35 cm and was maintained at 24 ± 2°C by an aquarium heater (Aquarium Systems, Italy) which was removed prior to testing. Nontoxic white watercolor paint (Rich Art Color Company Inc., Lod, NJ) was added to the water to make it opaque. The tank was located in the center of a small test room and was surrounded by many extramaze cues on the walls of the room and two on the rim of the tank, to provide both proximal and distal visual cues.

An automated tracking system (HVS Image Analysis VP-112, HVS Image, Hampton, England) recorded the position of the rat in the tank. A camera (Burle Security Products, Lancaster, PA) was mounted 1.4 meters above the surface of the water and was connected to a computer. Light was provided by four 40-watt bulbs, mounted in a square pattern, 1.2 meters above the surface of the water. A constant background noise was provided by a small radio.

The escape platform was made of transparent plastic (Lucite, DuPont, Wilmington, DE), and was 10 × 10 cm, with nine holes, 1 cm diameter, in the top to provide a gripping surface. The platform could be raised and lowered via a cable that ran along the bottom and ended outside of the tank. In its raised position, the platform was 2 cm beneath the surface of the water and the rat could escape from the water by climbing on it. In its lowered position, the platform was 19 cm beneath the surface of the water and unavailable for escape.

Procedure

Each rat was handled for 5 to 10 min a day during the 5 days prior to shaping. The shaping procedure trained the rats to escape from the water by climbing on the platform. The straight swim procedure trained them to swim to the platform when placed in the water (35). Both procedures were given for 1 day. Two days separated the straight swim and PD. PD, a spatial reference memory procedure, and RA, a spatial working memory procedure, were each given for 5 successive days, with 2 days separating the procedures.

Shaping. In the shaping phase, no spatial discrimination was required. A black curtain surrounding the tank eliminated visual extramaze cues. The experimenter stood inside of the curtain at the northeast side of the tank throughout the session. Two pieces of transparent plastic (Lucite), 128 cm long and 61 cm high, were placed parallel to each other in the water to form an alley, 14 cm wide. The top edges of the plastic extended 26 cm above the surface of the water. One end of the alley was placed against the edge of the tank. The other end of the alley extended into the middle of the tank and was closed by a third piece of transparent plastic (Lucite), 14 cm wide, 61 cm high, and 26 cm above the surface of the water. The platform was placed in its raised position about 30 cm from this end of the alley. Ten trials were given. For the first two trials, the rat was placed on the platform for 10 to 15 s. During trials 3 to 10, the rat was placed in the water at distances progressively further from the platform (closer to the edge of the tank) and allowed to swim to the platform. Two trials were given at each distance. The final distance was halfway between the platform and the edge of the tank. If the platform was not located in 10 s, then the experimenter led the rat to the platform. The intertrial interval (ITI) was 2 to 3 min.

Straight swim. Again, no spatial discrimination was required. The apparatus and experimenter location were identical to that in the shaping procedure. Each rat was placed in the water at the end of the alley next to the edge of the tank and allowed to
swim to the platform. Six trials were given. The time to reach the platform was recorded. If the platform was not located in 60 s, then the experimenter led the rat to the platform. The ITI was 2 to 3 min.

**Place discrimination.** The apparatus was the same as in shaping and straight swim except that the black curtain and Lucite alley were removed from the tank. The experimenter stood next to the tracking system in the southeast corner of the room throughout all trials. The tank was divided into four quadrants (NW, NE, SW, and SE) by two imaginary perpendicular lines crossing in the center of the tank. The platform was placed in the SW quadrant of the tank, 40 cm from the edge. Rats were placed in the water at one of three possible start locations, with one location in each of the three quadrants not containing the platform. Each start location was located in the middle of a quadrant at the edge of the tank.

One session consisting of 6 trials was given each day for 5 consecutive days. A trial began by placing the rat into the water facing the center of the tank at one of three start locations (as just described) around the edge of the tank. The sequence of start locations was chosen in a pseudorandom manner such that the start location in any given trial was different from that in the previous trial and each location was used twice during the session, once during the first 3 trials and once during the second 3 trials. The same sequence of start locations was used for all rats within a session but the sequence differed between sessions. The trial ended when the rat found the platform, or in 60 s, whichever came first. If the platform was not located in 60 s, the experimenter led the rat to the platform. The rat remained on the platform for 10 s, and was then placed in a holding cage for an ITI of 3 to 4 min. During the first five trials (platform trials), the platform was in its raised position, and available for escape. The sixth trial of each session was a variable-interval (VI) probe trial in which the platform was lowered and unavailable to the rat for a variable interval of time at the beginning of the trial (35). Intervals of 10, 20, 30, and 40 s were varied pseudorandomly so that the interval in a given trial was different from that in the previous probe trial. The same interval was used for all rats in a given session. When the VI ended, the platform was raised and the rat was allowed to find the platform. Performance in both platform trials and VI probe trials was used to assess spatial reference memory.

**Repeated acquisition.** The apparatus and experimenter location were the same as in PD. This procedure was similar to PD except that the location of the platform in the tank was different for each session. Within a session, the platform was located in one of the four quadrants (NW, NE, SW, or SE) and at one of three distances from the edge of the tank (20, 40, or 60 cm). The platform location remained the same throughout the entire session. Between sessions, the platform location was varied so that the platform was located in a different quadrant and at a different distance from the edge of the tank than in the previous session. The start locations used also varied between sessions so that in each session, the start location in the quadrant containing the platform was not used. The duration of each trial and ITI remained the same as in PD. One session was given each day for 5 consecutive days. As in PD, Trials 1 to 5 of each session were platform trials and Trial 6 was a VI probe trial. Spatial working memory was assessed during Trial 2 of RA. Spatial reference memory was assessed during Trials 4 and 5 (both platform trials) and Trial 6 (the probe trial).

**Measures of performance.** Three measures of performance were analyzed for platform trials in both PD and RA. Swim time was the time, in seconds, to reach the platform. Swim distance was the distance, in centimeters, of the path between the start location and the platform. Heading angle was the angle, in degrees, between the direction when leaving the edge of the tank, and a straight line drawn from the start location to the platform. For all three measures, lower scores indicated better performance.

Three measures of performance were analyzed for VI probe trials in both PD and RA. Quadrant time was the percentage of time spent in the quadrant containing the platform. Annulus time was the percentage of time spent within a circle 40 cm in diameter, centered on the location of the platform during the platform trials. Platform crossings was the number of times per 10 s that the rat crossed the 10 × 10 cm location of the submerged platform. To correct for variations in the duration of the probe trial among sessions, the number of crossings made during each probe trial was divided by 10 to yield the number of crossings per 10 s. For all three measures, higher scores indicated better performance.

**Data Analysis**

Data analyses were performed with SYSTAT 5.0 (SYSTAT Inc., Evanston, IL) and SAS 6.06.01 (SAS Institute Inc., Cary, NC). Based on the substantial evidence in the literature for age-related declines in learning and memory (15,16,18–25,35), conservative corrections to control familywise error rate were not made. Therefore, the significance level for all statistical tests was set at 0.05.

**Straight swim.** A one-way analysis of variance (ANOVA) was performed on Trial 6 to determine whether swim times among the four age groups differed by the end of training. Effects of age across the session were assessed by an ANOVA with trials as the repeated measure. Differences between all age groups were assessed by planned contrasts.

**Place discrimination.** For platform trial measures, the mean of Trials 1–5 for each session was calculated for each rat, yielding 5 values (1 per session) for each measure per rat. For VI probe trials, the individual probe trial measures obtained in each session were used in the data analysis. A one-way ANOVA with repeated measures was performed for each measure with sessions as the repeated measure. Planned contrasts assessed differences between all age groups.

**Repeated acquisition.** The data from RA were analyzed in two different ways. First, each of the 6 trials was averaged across all 5 sessions as a means of assessing spatial working and reference memory. Second, performance across all trials and sessions was analyzed in a manner similar to PD to assess overall spatial memory deficits.

Spatial working memory was assessed in Trial 2 of Sessions 1 to 5. Each rat had three Trial 2 measures: one for swim time, swim distance, and heading angle. The mean of each age group was calculated for each of these three Trial 2 measures. Age effects on each measure were assessed by a one-way ANOVA and differences between the age groups were assessed by planned contrasts.

Spatial reference memory was assessed in Trials 4, 5, and 6 of Sessions 1 to 5. Trials 4 and 5 were platform trials, so data from these trials were combined to form a single mean for each of the three platform trial measures. Each rat had three combined Trials 4 and 5 measures: one for swim time, swim distance, and heading angle. These values were used in the principal components analysis only. Trial 6 was analyzed separately because it was a probe trial (see below).

The second type of analysis examined performance across all
trials and sessions to assess spatial memory in general. For platform trial measures, the mean of each trial across Sessions 1 to 5 was calculated for each rat, yielding 5 values (1 per trial) for each measure per rat. This analysis examined improvement within a session, rather than between sessions as in PD, to assess learning of a new platform location. Probe trial (Trial 6) measures were analyzed in the same manner as PD probe trial measures. One-way ANOVAs were performed for each measure with trials as the repeated measure for platform trials and sessions as the repeated measure for probe trials. Planned contrasts were performed in the same manner as in PD.

**Principal Components Analysis**

Principal components analysis (PCA) has been used in studies of aged humans to differentiate between measures of different memory systems (37). The same type of analysis has not been utilized in previous studies of memory in aged rats. PCA was used in this study as a means of distinguishing between the operationally defined spatial reference and working memory measures of performance.

Before undertaking the PCA, mean values representing either initial or asymptotic performance were computed for each measure. For each PD platform trial measure, the score entered into the PCA was the mean of all platform trials in Sessions 4 and 5. For each PD probe trial measure, the score entered was the mean of the two probe trials in Sessions 4 and 5. Thus, the calculated values for PD represented performance at the end of PD testing, at which point the 4MO group was at or near asymptotic levels of performance. For each RA platform trial measure, the score entered was the mean of Trials 4 and 5 in Sessions 1 to 5 as calculated above. These values represented near asymptotic performance for the 4MO group at the end of a session. For each RA probe trial measure, the score entered was the mean of probe trials from Sessions 1 to 5, representing performance at the end of each RA session. For RA Trial 2 measures (swim time, swim distance, and heading angle), the mean of Trial 2 in Sessions 1–5 was entered, representing initial performance after the information trial.

This set of 15 mean scores was entered into a PCA in SAS. A two-factor solution was chosen a priori, based on the assumption that the variables would resolve onto two components, one representing reference memory, the other representing working memory. The initial factor pattern was rotated using an oblique PROMAX algorithm. The data were reanalyzed with a VARI MAX rotation if the correlation between components was less than 0.3.

**RESULTS**

**Subjects**

None of the rats tested had obvious health problems (e.g., cataracts, glaucoma, or debilitating tumors) that would have interfered with behavioral testing. Three 24MO rats died during the experiment yielding a mortality rate of 11.5% for this group. All other rats were healthy and completed experimental testing.

**Straight Swim**

Age did not significantly affect swim time in Trial 6, suggesting no differences in swimming ability at the end of testing (Fig. 1). However, planned contrasts indicated that 24MO were significantly different from 11MO in Trial 6 ($p < 0.03$). Swim time across Trials 1 to 6 was significantly affected by Age, $F(3, 91) = 5.057$, $p < 0.004$. Swim time improved within the session, as indicated by a significant main effect of Trial, $F(5, 455) = 10.189$, $p < 0.001$. The overall age effect was due to the significant difference between 11MO and 24MO, as assessed by a planned contrast ($p < 0.05$). No other planned contrasts were significant.

**Place Discrimination**

A summary of deficits relative to the 4MO group in all measures of PD is presented in Table 1.

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**TABLE 1**

**SUMMARY OF AGE-RELATED DEFICITS IN PD AND RA RELATIVE TO THE 4MO GROUP**

<table>
<thead>
<tr>
<th>Measure</th>
<th>All PD Trials</th>
<th></th>
<th>RA Trial 2</th>
<th></th>
<th>All RA Trials</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>11MO</td>
<td>17MO</td>
<td>24MO</td>
<td>11MO</td>
<td>17MO</td>
<td>24MO</td>
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<tr>
<td>Swim time</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Swim distance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Heading angle</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Annulus-40 time</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Quadrant time</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

An X indicates the presence of a significant impairment relative to the 4MO group.
AGE-RELATED MEMORY DEFICITS IN RATS

**Figure 2**. Platform trial performance in place discrimination as assessed by swim time (A), swim distance (B), and heading angle (C). Each point represents the mean group performance (± SEM) in Trials 1-5 of each session. Values for all three measures increased with increasing age.

**Heading angle.** As age increased, heading angle increased, $F(3, 92) = 4.32, p < 0.008$ (Fig. 2C). Heading angle decreased throughout testing [main effect of Session, $F(4, 368) = 84.347$, $p < 0.001$]. The Session × Age interaction was not significant. 24MO were impaired relative to 4MO ($p < 0.04$) and 11MO ($p < 0.004$) but not to 17MO.

**Probe trial measures: Quadrant time.** As age increased, the percentage of time spent in the quadrant containing the platform decreased, $F(3, 92) = 37.181, p < 0.001$ (Fig. 3A). Quadrant time significantly increased throughout testing, $F(4, 368) = 102.910$, $p < 0.001$. The rate of improvement among the groups differed as demonstrated by a Session × Age interaction, $F(12, 368) = 6.834$, $p < 0.001$. 24MO were impaired relative to all other age groups ($p$'s < 0.001). 17MO were impaired relative to 4MO ($p < 0.002$).

**Platform trial measures: Swim time.** As age increased, swim time increased, $F(3, 92) = 34.999$, $p < 0.001$ (Fig. 2A). Swim time decreased throughout testing [main effect of Session, $F(4, 368) = 162.865$, $p < 0.001$], and the rate of learning differed among the groups as indicated by a significant Session × Age interaction, $F(12, 368) = 4.448$, $p < 0.001$. 24MO were impaired relative to all other age groups ($p$'s < 0.001). 17MO were impaired relative to 4MO ($p < 0.04$). 11MO were not significantly impaired relative to 4MO. 11MO and 17MO did not significantly differ from each other on swim time or any other PD measure.

**Swim distance.** Age had a significant effect on swim distance, as demonstrated by a significant Session × Age interaction, $F(12, 368) = 9.099$, $p < 0.001$ (Fig. 2B). Swim distance decreased throughout testing [main effect of Session, $F(4, 368) = 240.421$, $p < 0.001$], however, the main effect of Age was not significant. 24MO were impaired relative to all other age groups ($p$'s < 0.002), and 17MO were impaired relative to 4MO ($p < 0.04$).

**Figure 3**. Probe trial performance in place discrimination as assessed by quadrant time (A), annulus-40 time (B), and platform crossings (C). Each point represents the mean group performance (± SEM) in Trial 6 of each session. Values for all three measures decreased with increasing age.

**Session**
**Annulus-40 time.** As age increased, the percentage of time spent in the 40 cm annulus decreased, $F(3,92) = 39.665$, $p < 0.001$ (Fig. 3B). Annulus-40 time significantly increased throughout testing, $F(4,368) = 125.298$, $p < 0.001$, however, the rate of improvement was different among the groups [significant Session $\times$ Age interaction, $F(12, 368) = 6.901$, $p < 0.001$]. 24MO were impaired relative to all other age groups ($p^{''}s < 0.001$). 17MO were impaired relative to 4MO ($p < 0.002$).

**Platform crossings.** As age increased, the number of platform crossings made per 10 s decreased, $F(3, 92) = 32.353$, $p < 0.001$ (Fig. 3C). Platform crossings significantly increased throughout testing, $F(4, 368) = 19.76$, $p < 0.001$, however, the rate of improvement was different among the groups [significant Session $\times$ Age interaction, $F(12, 368) = 2.601$, $p < 0.003$]. 24MO were impaired relative to 11MO and 4MO ($p^{''}s < 0.002$) but not to 17MO. 11MO and 17MO had fewer crossings relative to 4MO ($p < 0.002$ and $p < 0.001$, respectively).

**Repeated Acquisition**

Table 1 presents a summary of deficits relative to the 4MO group in all RA measures.

**Trial 2 measures.** Swim time was impaired in the 24MO group (Fig. 4). The main effect of Age was significant for swim time, $F(3, 92) = 12.538$, $p < 0.001$. 24MO had significantly higher swim times than all other age groups ($p^{''}s < 0.003$). The 17MO, 11MO, and 4MO groups were not significantly different from each other. Swim distance and heading angle in Trial 2 were not significantly affected by age.

**Platform trial measures, All trials: Swim time.** Swim time increased with age, $F(3, 92) = 23.87$, $p < 0.001$ (Fig. 5A). Swim time decreased throughout the session [main effect of Trial, $F(4, 368) = 132.561$, $p < 0.001$], but the decreases in swim time differed between groups [significant Trial $\times$ Age interaction, $F(12, 368) = 4.807$, $p < 0.001$]. 24MO were impaired relative to all other age groups ($p^{''}s < 0.001$). 17MO were impaired relative to 4MO ($p < 0.04$). 11MO and 17MO were not significantly different from each other in swim time or any other RA measure.

**Swim distance.** Age significantly affected swim distance, as demonstrated by a significant Trial $\times$ Age interaction, $F(12, 368) = 7.672$, $p < 0.001$ (Fig. 5B). Swim distance decreased throughout the session [main effect of Trial, $F(4, 368) = 66.704$, $p < 0.001$], however, the main effect of Age was not significant. 24MO were significantly impaired relative to 11MO and 4MO ($p < 0.009$ and $p < 0.001$, respectively) but not to 17MO. 17MO were impaired relative to 4MO ($p < 0.03$).

**Heading angle.** Heading angle was significantly increased by Age, $F(3, 92) = 5.605$, $p < 0.002$, and Trial, $F(4, 368) = 5.728$, $p < 0.001$ (Fig. 5C). The Trial $\times$ Age interaction was also significant, $F(12, 368) = 1.802$, $p < 0.05$. 24MO were impaired relative to all age groups ($p^{''}s < 0.04$). 17MO, 11MO, 4MO were not significantly different from each other.

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**FIG. 4.** Spatial working memory performance as assessed by swim time in Trial 2 of repeated acquisition (mean $\pm$ SEM). An asterisk indicates a significant impairment relative to the 4MO group.

**FIG. 5.** Platform trial performance in repeated acquisition as assessed by swim time (A), swim distance (B), and heading angle (C). Each point represents the mean group performance ($\pm$ SEM) in one trial across Sessions 1 to 5. Values for swim time and swim distance increased with increasing age.
**Probe trial measures, All Sessions: Quadrant time.** Quadrant time decreased as age increased, $F(3, 92) = 24.395$, $p < 0.001$ (Fig. 6A). Session significantly affected quadrant time, $F(4, 368) = 37.050$, $p < 0.001$. The Session × Age interaction was also significant, $F(12, 368) = 2.085$, $p < 0.02$. 24MO were impaired relative to all other age groups ($p's < 0.003$). 17MO were impaired relative to 4MO ($p < 0.003$).

**Annulus-40 time.** As age increased, annulus-40 time decreased, $F(3, 92) = 30.185$, $p < 0.001$ (Fig. 6B). Session significantly affected annulus-40 time, $F(4, 368) = 4.38$, $p < 0.003$, however, the Session × Age interaction was not significant. 24MO were impaired relative to all other age groups ($p's < 0.002$). 17MO were impaired relative to 4MO ($p < 0.003$).

**Platform crossings.** Platform crossings decreased as age increased, $F(3, 92) = 26.394$, $p < 0.001$ (Fig. 6C). The Session effect and interaction were not significant. 24MO were impaired relative to all other age groups ($p's < 0.001$). 17MO and 11MO were impaired relative to 4MO ($p < 0.003$ and $p < 0.04$, respectively).

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**Homogeneity of Variance**

In order to determine whether the magnitude of individual variation within the 24MO group was significantly greater than in the 4MO group, Hartley’s $F_{max}$ test of homogeneity of variance (52) was performed between these groups for each cognitive measure. For all PD measures, two sets of values were calculated. To examine initial performance, the value used was the mean of each measure from Sessions 1, 2, and 3. To examine asymptotic performance, the value used was the mean of each measure from Sessions 4 and 5. For RA platform trial measures, the value used was the mean of each measure from Trials 4 and 5, or the mean from Trial 2. For RA probe trial measures, the value used was the mean of each measure from Sessions 1 to 5. The critical value for $F_{max}$ at the 0.05 level with 30 df was 2.07. The $F_{max}$ indicated that the 24MO group had a significantly larger variance than the 4MO group in swim time in PD for Sessions 4 to 5 only $(F_{max} = 2.67)$. All other measures had nonsignificant $F_{max}$ values or values in which the variance of the 4MO group exceeded that of the 24MO group (annulus-40 time in Sessions 1 to 3 of PD, platform crossings in Sessions 1 to 3 and 4 to 5 of PD, and platform crossings in RA).

**Principal Components Analysis**

The eigenvalues for both factors were greater than 1 (8.74 and 1.45, respectively). The percent of variance accounted for by Factors 1 and 2 was 58% and 10%, respectively. Following a PROMAX rotation, the two factors were highly correlated ($r = 0.51$). Because of the high correlation between the factors, the factor solution was not reanalyzed with a VARIMAX rotation. The pattern loadings of the variables onto the rotated components are presented in Table 2, and a correlation matrix of the variables entered into the PCA is presented in Table 3.

Most variables loaded highly onto Factor 1 (Table 2). All of the PD measures (except PANGAV) and the RA probe trial measures loaded highly onto Factor 1. PANGAV did not load highly onto either factor. The working memory measures RLATT2 and RDST2 loaded higher on Factor 2 than on Factor 1. RANGT2 did not load highly on either factor.

**Discussion**

**Spatial Reference Memory**

Aging significantly affected performance in all measures of PD. 24MO rats had a severe spatial reference memory deficit as indicated by a significant impairment relative to 4MO in all platform and probe trial measures. 17MO had a less severe, yet substantial, spatial reference memory deficit as indicated by impairments on some platform and all probe trial measures. 11MO rats had a mild spatial reference memory deficit as indicated by an impairment in platform crossings only. These data are in accordance with other studies demonstrating age-related PD impairments in Fischer-344 (10,32,33,34) and other rat strains (2,15,18,19,21,50), and suggest that the age-related decline in spatial reference memory from young adulthood to old age is nonlinear.

Only recently has data been available regarding the spatial reference memory abilities of mature adult (11- to 12-month-old) rats. Fischer et al. (15) did not observe significant differences between 3- and 12-month-old Sprague-Dawley rats in platform trials (using swim time and swim distance measures) and in one probe trial measure (percent of swim path spent in the correct quadrant). However, the 12-month-old rats were impaired on
TABLE 2

COMPONENT LOADINGS FOR COGNITIVE MEASURES

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Loadings higher than 0.5 are highlighted in bold type.

The platform crossings measure during the probe trial. These data are consistent with our findings that 11-month-old Fischer-344 rats are impaired in the platform crossings measure only. Note that the platform crossings measure is the most challenging measure recorded in either study because it requires precise localization of the platform. Both studies indicate the presence of a spatial reference memory deficit in rats as young as 11 to 12 months of age but illustrate that only difficult measures of performance are sensitive enough to detect age-related impairments in these rats.

The performance of 11- to 12-month-old rats (and 17- to 18-month-old rats, see below) in the study by Fischer et al. (15) and in the present study are very similar. However, note that the probe trials used in the studies were quite different. Fischer et al. used one no-platform (NP) probe trial at the end of PD testing in which the platform was removed from the tank for 60 s. The present study used five VI probe trials throughout testing, one at the end of each daily session. Because the VI probe trial is a more sensitive measure of spatial memory than the traditional NP probe trial (35), the results from the VI probe trial may be a more accurate reflection of age-related mnemonic changes than those obtained with the NP procedure.

The mnemonic impairments observed in the 17MO group are similar to those observed in previous studies. Eighteen-month-old Sprague-Dawley rats in the study by Fischer et al. (15) were not significantly different from 3-month-old rats in platform trials but were impaired in both probe trial measures. In a different study (10), significant differences were not observed between 4- and 16-month-old Fischer-344 rats in platform trials (swim time and swim distance) but were observed in quadrant time during probe trials. The results of these two studies are consistent with those of the present study, in that deficits in swim distance on platform trials were absent, but deficits in probe trials were present. However, it is interesting that neither study reported an age-related deficit in swim time similar to the one observed in this study. Although the reason for this discrepancy is not clear, it is possible that differences in strain or chronological age may have affected the results (see below).

Although results from a number of studies are consistent, comparisons between rats of different strains at similar chronological ages must be made with caution. Different strains of rats have different life spans which may influence the age at which behavior and neurobiology are affected by aging. Thus, definitions of "old" based on chronological age may be misleading (9) because different strains of rats at the same chronological age may not be behaviorally or neurobiologically equivalent. For example, 12MO and 24MO Fischer-344 rats performed worse in PD in the water maze than 12MO and 24MO rats that

TABLE 3

CORRELATION MATRIX FOR COGNITIVE MEASURES

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were a cross between Brown-Norway and Fischer-344 (34). In another study, 28MO Long-Evans rats did not have a spatial memory impairment in the water maze, whereas 28MO Fischer-344 rats could not even complete the same task because they could not swim well enough to prevent themselves from drowning (33). In terms of neurobiology, Wistar–Kyoto rats, which have a shorter life span than Brown-Norway rats, have more extensive degeneration of septohippocampal cholinergic neurons earlier in life than do Brown-Norway rats (26). Whereas these few examples are not meant to discourage comparisons among strains, they illustrate that all rat strains are not created equal and that direct comparisons between chronologically similar age groups of different strains should be made with caution.

The probe trials in both PD and RA illustrate the utility of using multiple measures of performance to examine behavior. During the platform trial, a rat can use one of several strategies (e.g., circling the tank at a certain distance from the edge of the tank) to locate the platform. The probe trials require memory for the precise location of the platform, so they more reliably assess the accuracy of spatial memory than platform trial measures. The probe trial measures indicated a more linear decline in mnemonic ability with age, whereas the platform trial measures indicated a decline in mnemonic ability at or beyond 17 months of age. This result suggests that probe trials can discriminate among age groups better than platform trials and may be more sensitive tests of age-related mnemonic impairments.

**Spatial Working Memory**

Spatial working memory deficits were present only in 24MO rats. This result is consistent with a study in which 24MO Wistar rats were impaired relative to 3MO rats in a different RA procedure (50). Similar results were obtained when 3MO, 12MO, and 22MO Fischer-344 rats were trained on a spatial delayed matching-to-sample water-escape working memory task (36). 22MO rats were impaired relative to both 12MO and 3MO rats in both trials to criterion and errors during acquisition of the task. The 12MO and 3MO rats were not significantly different from each other on either measure. When tested with retention intervals ranging from 5 to 120 min, the 22MO rats made significantly fewer correct choices across all retention intervals than both the 12MO and 3MO groups. Together, these results suggest that spatial working memory deficits are present only in 22-24MO rats.

Two other previous studies indicated that spatial working memory deficits may be present in younger rats. Both 16MO and 24MO Fischer-344 rats tested in a working memory procedure similar to RA had impaired swim distance relative to 2.5MO rats (32). Spatial working memory deficits were also found in 12MO, 17MO, and 24MO Wistar rats tested in an 8-arm radial maze (31). The three age groups were impaired relative to the 3MO group in all measures of performance (choice accuracy, percent errors, and total time to completion). Chronological age, task, or procedural differences may account for the inconsistent results among the studies of intermediate-aged rats.

Prior experience in PD influenced performance in RA in two ways. First, because of age-related deficits in PD, performance among the groups may not have been equal at the beginning of RA. PD presumably facilitated RA performance in the 4MO group, which may have influenced the magnitude of the observed age-related deficits in RA. However, during Trial 1, there was no significant difference in swim time (Fig. 5A) among the groups, suggesting that all ages began each session of RA at a similar level. Second, because the platform location during Session 3 of RA (SW quadrant, 20 cm from the edge of the tank) was similar to the PD platform location (SW quadrant, 40 cm from the edge of the tank), it is possible that memory for that quadrant may have biased the amount of time spent in this quadrant. All age groups had significantly higher quadrant times in Session 3 than in Sessions 2 or 4 (one-way ANOVAs, all p’s < 0.04). This pattern suggests the presence of a bias toward the PD platform location. However, similar increases were not present in the annulus-40 time or platform crossings measures, suggesting that if a bias does occur, then it is not sufficiently strong to be detected by more challenging measures of mnemonic ability. If PD continues to precede RA in future testing, then use of the PD platform location should be discontinued. The length of time required to learn RA when not preceded by PD, and the time required for 24MO rats to master RA, will need to be determined in future studies.

Manipulations of task demand should influence the observation of deficits in RA. Increasing task demand in a delayed-non-match-to-sample procedure in a Y maze increased the magnitude of age-related deficits observed (1). Increasing task demand in RA by increasing the retention-interval between Trials 1 and 2, increasing the number of platform locations to be remembered within a session, or introducing a type of working memory probe trial may increase the likelihood of observing spatial working memory deficits at younger ages (45).

Working memory was defined earlier as memory that is useful for one trial only. In the present study, the choice of Trial 2 as the measure of working memory was based on measures used in the delayed conditional discrimination (DCD) paradigm (44). In a DCD procedure, working memory is assessed by performance in a choice trial which follows an information trial. Because Trials 1 and 2 are analogous to the information and choice trials, working memory was assessed in Trial 2 of RA. Trials 3 to 6 of RA should not assess working memory. It is unclear what type of memory Trial 3 measures, but it is possible that Trial 3 may be a transitional trial in which memory required for the task shifts from working to reference. However, by Trial 4, the platform has been encountered three times in its new location, so Trials 4 to 6 should assess mainly reference memory. The principal components analysis supports this hypothesis (see below).

**Principal Components Analysis**

Spatial reference and working memory measures were distinct, as indicated by the principal components analysis. Performance during Trial 2 of RA reflected memory for the platform location after only one exposure to the new location, so it relied heavily on working memory. Performance in Trials 4, 5, and 6 of RA reflected memory for the new platform location after several exposures, and thus, should have relied more on reference memory than working memory. The factor loadings supported this hypothesis. It is clear that Factor 1 was associated with variables from PD and RA that required reference memory and Factor 2 was associated with measures from Trial 2 of RA but not with other measures that required reference memory. This suggests that Trial 2 measures assessed a facet of cognitive ability distinct from that assessed by the other measures of performance, which is consistent with the hypothesis that Trial 2 measures assess working memory, whereas PD and other RA measures assess reference memory.

Heading angle in Trial 2 of RA did not load well onto either factor and heading angle from Trials 4 to 5 of RA loaded better onto the working memory factor (Factor 2) than the refer-
ence memory factor (Factor 1). A comparison of heading angle to other measures of platform trial performance in RA suggests that heading angle may not improve as quickly as swim time or swim distance during RA (Fig. 5), and that more learning may be required to score well on this measure than is possible during each session of RA. This may explain why the loading pattern of heading angle was not consistent with that of the other platform trial measures.

The fact that the two factors are correlated and the first factor accounts for over 50% of the total variance indicates that the reference and working memory measures were not completely independent. The correlation may be the result of the common spatial component of the PD and RA tasks, in which case the observed impairments in PD and RA may reflect a more general impairment of spatial processing ability. Tests of non-spatial working and reference memory may help to elucidate the effects of aging on each type of memory specifically. Testing rats in PD, RA, other traditional spatial working memory tasks (e.g., a radial arm maze or a T-maze alternation task), and nonspatial working memory tasks (e.g., an enclosed radial arm maze with distinctive intra-maze cues) may clarify the issue. If the PCA distinguishes between reference and working memory processes (rather than between other processes such as spatial and nonspatial), then the measures of performance from the nonspatial working memory task should load onto a factor with the measures from Trial 2 of RA, separate from other measures of performance in PD and RA. This pattern would provide further support for the operational distinctions between reference and working memory in RA. The present results illustrate that principal components analysis can be a useful tool for differentiating among measures of different mnemonic processes. Future work will determine whether this type of analysis can generalize to other measures of the same mnemonic processes.

Individual Differences in Performance

Many recent studies have indicated that increased variability in learning and memory function is characteristic of aged rats, monkeys, and humans (15, 21; see also 41, 47 for reviews). Differences in variance in the cognitive measures for the 4MO and 24MO groups in this study were examined to assess possible increases in variability in the aged population. The variance of the 24MO group was significantly greater than that of the 4MO group in only one measure, swim time in PD. In most other measures, the 4MO and 24MO groups were similarly heterogeneous. This was true for measures that assessed both initial learning (Sessions 1 to 3 of PD, Trial 2 of RA) and asymptotic learning (Sessions 4 to 5 of PD), suggesting that the range of individual differences within the aged population was not substantially different from that of the young population. Although the data cannot address the existence of individual differences in effects of aging on performance or variability in the rate of learning (22), they conflict with the assumption that aged populations demonstrate increased variability in performance as compared to young populations. Other studies using different rat strains have demonstrated marked increases in variance within the aged population (22). This discrepancy may be related to the strain of rat or the particular testing procedures used in the present study, and raises the possibility that individual differences in the effects of aging manifest themselves differently in different rat strains.

Sensorimotor Effects

Because aging can affect sensorimotor, as well as cognitive ability, it is possible that nonmnemonic deficits contribute to observed deficits on PD and RA. Two lines of evidence suggest that this was not the case. The first is the pattern of age-related impairments. It is sometimes noted that swim time can be confounded by age-related declines in sensorimotor ability such as swim speed (32, 50). Swim distance is frequently measured instead because it supposedly eliminates any possible bias due to differences in swim speed. In this study, robust age-related deficits occurred in swim time, whereas age-related deficits in swim distance were minimal. This discrepancy raises the possibility that our age-effects were not solely mnemonic in origin. The probe trial measures refute this possibility and serve to illustrate the utility of multiple measures of performance. The probe trial measured the accuracy of memory, rather than measuring strategies for finding the platform. None of the probe trial measures were confounded with swim speed because an accurate rat with slow swim speed could still score well on any of the three measures. Robust age-related deficits occurred in all three probe trial measures in both PD and RA, suggesting that the observed deficits in PD and RA were truly mnemonic in origin rather than motoric.

The other line of evidence is the straight swim, which can measure sensorimotor ability in the water. Swim time throughout the trials decreased from Trial 1 to Trial 6 in all groups, such that by the end of the session, no significant differences were present among the groups. The absence of significant differences relative to the 4MO group in swim time on Trial 6 suggests that the older rats did not have impaired swimming ability and that the observed age-related impairments in PD and RA were due to mnemonic deficits rather than to differences in swimming ability. The results of straight swim do not exclude age-related deficits in visual acuity as an explanation for the apparent cognitive deficits in aged rats. However, a recent study demonstrated no significant difference between 6MO and 27MO female Fischer-344 rats in performance of a visible-platform task in the water maze (3), suggesting that potential deficits in visual acuity do not significantly contribute to observed age-related impairments.

CONCLUSION

In summary, the results of the present study are important for six reasons. First, spatial reference memory deficits were observed in rats as early as 11 months of age, suggesting a nonlinear pattern of age-related spatial reference memory deficits in Fischer-344 rats. Second, both spatial reference and working memory deficits were observed in 24-month-old Fischer-344 rats. Third, the repeated acquisition procedure was sufficiently sensitive to detect age-related mnemonic impairments. Fourth, the variable-interval probe trials were more sensitive to age-related mnemonic changes than were the platform trials. Fifth, the variability in performance of the 24-month-old group was not significantly higher than that of the 4-month-old group. Sixth, principal components analysis was a useful means of distinguishing between measures of different mnemonic processes in rats.

ACKNOWLEDGEMENTS

We thank S. Golski and R. Wan for their assistance with behavioral testing of the rats, S. Breecker, D. Serans, and C. Gray for statistical assistance, and K. Pang, L. Gorman, and J. Chrobak for comments on the manuscript. This research was supported by NIA grant AG 05146 and ADRC grant NS 20471 to D.L.P. and partially by grants from The Du Pont Merck Pharmaceutical Company and G. D. Searle & Company to D.S.O.
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